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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/996,357	11/27/2001	Malcolm L. Geffer	PPI-105	1918
959	7590	04/23/2004	EXAMINER	
LAHIVE & COCKFIELD, LLP. 28 STATE STREET BOSTON, MA 02109			NICHOLS, CHRISTOPHER J	
			ART UNIT	PAPER NUMBER
			1647	

DATE MAILED: 04/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/996,357

Applicant(s)

GEFTER ET AL.

Examiner

Christopher J Nichols, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 February 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-78 is/are pending in the application.
- 4a) Of the above claim(s) 1-73, 77 and 78 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 74-76 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claim(s) 1-78 are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 27 November 2001 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group V (Claims 74-76) in the Response filed 17 February 2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Sequence Rules

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth herein. This application discloses an amino acid and nucleic acid sequences in Figures 3-7, pp. 4 line 29, pp. pp. 16 lines 8 & 28, pp. 17 line 27, pp. 18 line 13. Correction is required.

Drawings

3. The drawings are objected to because Figure 2 contains 12 panels none of which are labeled (i.e. "12A-12L"), Figure 8 contains two graphs and should be labeled "8A" and "8B". A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Specification

4. The disclosure is objected to because of the following informalities: U.S. Patent Applications Nos. 08/548,998 and 08/616,081 are now both abandoned. Applicant is invited to update the status of these applications (pp. 14 line 21). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims **74-76** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *a method for preparing A β (16-30)-hFc*, does not reasonably provide enablement for *preparing any therapeutic agents, any as of yet unspecified peptide-target protein combinations, or any agents containing D-amino acids*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **make** or **use** the invention commensurate in scope with these claims.
6. The claims are drawn very broadly to a method of preparing a therapeutic agent comprising an immunoglobulin heavy chain fused via a linker or a direct bond to a peptide capable of binding a target protein. The language of said claims encompasses all known and unknown proteins which may be targets for an as of yet unidentified peptide.
7. The specification prophetically considers a therapeutic agent comprising an immunoglobulin heavy chain fused via a linker or a direct bond to a peptide capable of binding a target protein. The Specification teaches the manufacture of a fusion protein comprising A β (16-

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30) fused to the N-terminus of a peptide consisting of the human IgG1 Fc domain and hinge region (A β (16-30)-hFc) domain (Example 8). A β (16-30)-hFc was administered to a mouse transgenic for both the Swedish mutation of amyloid precursor protein (APP) and presenilin M146L by direct infusion into the cerebral cortex in one hemisphere (Example 9). The mouse was scarified and the amount of amyloid in brain sections was determined by Thioflavin S staining. The plaque burden at the site of infusion was significantly decreased compared to the contra-lateral control hemisphere (Figure 10).

8. However, the specification fails to provide any guidance for the successful manufacture and/or use of a therapeutic agent comprising an immunoglobulin heavy chain fused via a linker or a direct bond to a peptide capable of binding a target protein other than A β (16-30)-hFc. Since the resolution of the various complications in regards to making and using a therapeutic agent comprising an immunoglobulin heavy chain fused via a linker or a direct bond to a peptide capable of binding a target protein is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of formulations therapeutic agent comprising an immunoglobulin heavy chain fused via a linker or a direct bond to a peptide capable of binding a target protein. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed. In addition, A β (16-30)-hFc does not contain any D-amino acids.

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9. Additionally, a person skilled in the art would recognize that predicting the efficacy of using therapeutic agent comprising an immunoglobulin heavy chain fused via a linker or a direct bond to a peptide capable of binding a target protein *in vivo* based solely on A β (16-30)-hFc and the hypothesized performance of others is highly problematic (see MPEP §2164.02). Thus, although the specification prophetically considers and discloses general methodologies of using the claimed methods in *in vivo* therapies, such a disclosure would not be considered enabling since the state of protein biochemistry as it pertains to therapeutic agent comprising an immunoglobulin heavy chain fused via a linker or a direct bond to a peptide capable of binding a target protein is highly unpredictable. The factors listed below have been considered in the analysis of enablement [see MPEP §2164.01(a) and *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)]:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

10. The following references are cited herein to illustrate the state of the art of protein biochemistry.

11. On the breadth of the claims, the skilled artisan readily recognizes that protein chemistry is an unpredictable area of biotechnology. Proteins with deletion, insertion or substitution/replacement of single amino acid residues may lead to both structural and functional

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changes in biological activity and immunological recognition, see in particular Skolnick & Fetrow (2000) "From genes to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39. For example, Jobling & Holmes (1991) "Analysis of structure and function of the B Subunit of cholera toxin by the use of site-directed mutagenesis." Molecular Microbiology **5**(7): 1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which produce proteins that differ in native conformation, immunological recognition, binding and toxicity. The skilled artisan further recognizes that immunological responses may depend upon the structural characteristics (conformation) of the particular protein (amino acid sequence) targeted. Thus, both biological function and immunological recognition are unpredictable properties which must be experimentally determined. For instance, Stern *et al.* (May 1990) "Antibodies to the β -amyloid peptide cross-react with conformational epitopes in human fibrinogen subunits from peripheral blood." FEBS **264**:43-47 teaches that the anti-A β antibody, AMY 33 cross-reacts with fibrinogen (Table I, pp. 46). Thus absent sufficient guidance, a therapeutic agent such as an antibody can cross-react with unrelated proteins thus requiring additional experimentation to determine which epitopes on each and every amyloid protein can be used to make and use an antibody with sufficient specificity to the protein for which it is raised.

12. On the nature of the invention, the problem of predicting protein structure in the absence of specific data (guidance) and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of

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success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. However, Applicant has provided little or no guidance beyond the mere suggestion of mutating, truncating, and breaking the claimed proteins into "fragments" and "peptides" to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), the nature and extent of changes that can be made in these positions while remaining useful for making therapeutic antibodies. Although the specification cites art-recognized procedures for producing and screening for active muteins and therapeutic antibodies, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity and epitopes. This is of particular relevance when making antibodies, especially

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those required to practice a therapy. The art recognizes that function cannot be predicted from suggestion alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39, especially p. 36 at Box 2; Doerks *et al.*, (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427]. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen antibodies against the same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide antibodies with the necessary activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function as well as the resultant antibodies made from these mutants, fragments, and peptides, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed antibodies and method thereof in its full scope.

13. On the predictability of the art, specifically immunization using a therapeutic agent, Goldsby *et al.* (2002) Kuby Immunology 4th Ed. Chapter 18 "Vaccines" (pp. 449-465) teaches that passive immunization does not allow for the formation of immunological memory requiring

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continued dosages if the desired immunity is to be maintained. Also the issue of the antigenicity of the antibody administered must be taken into consideration because it can trigger and unwanted and possibly harmful immune response especially mouse antibodies administered to humans (pp. 451). Therefore inadequate guidance is presented in the Specification to overcome these obstacles in practicing the invention to the full scope as claimed.

14. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *suggestion* to the manufacture and use of therapeutic agent comprising an immunoglobulin heavy chain fused via a linker or a direct bond to a peptide capable of binding a target protein other than A β (16-30)-hFc as exemplified in the references herein.

15. Claims **74-76** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

16. The claims require a "therapeutic agent" but teach a method of identifying said agent thus implying that the activity and/or structure and/or identity of the agent used is not known and it must be discovered prior to preparing said agent. The claims do not require that the therapeutic agent to possess any particular conserved structure, or other distinguishing feature, such as a specific biological activity. Thus, the claims are drawn to a genus of agents that is defined by desired activity.

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17. Furthermore the art recognizes that “agent” can pertain to chemical entities, pharmaceutical compositions, proteins, peptides, non-peptide compounds, animal tissue extracts, nucleic acids, antisense molecules, peptidomimetic, transformed cells, radiation, antibodies, antibody fragments, cyclic peptides, agonists, antagonists, inhibitors, enhancers, vegetable extracts, cell extracts, synthetic agents, biologically derived substances as well as proteinaceous substances, known, and unknown compounds.

18. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is a recitation of desired activity. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. Accordingly, the specification does not provide adequate written description of the claimed genus.

19. To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. *Vas-Cath*, 935 F.3d at 1563; see also *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 [41 USPQ2d 1961] (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that “the inventor invented the claimed

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invention”); *In re Gosteli*, 872 F.2d 1008, 1012 [10 USPQ2d 1614] (Fed. Cir. 1989) (“the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed”). Thus, an applicant complies with the written-description requirement “by describing the invention, with all its claimed limitations, not that which makes it obvious,” and by using “such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention.” *Lockwood*, 107 F.3d at 1572.

20. See *University of Rochester v. G.D. Searle & Co.*, 68 USPQ2d 1424 (DC WNY 2003) and *University of Rochester v. G.D. Searle & Co. et al.* CAFC [(03-1304) 13 February 2004]. In *University of Rochester v. G.D. Searle & Co.* a patent directed to method for inhibiting prostaglandin synthesis in human host using an unspecified compound, in order to relieve pain without side effect of stomach irritation, did not satisfy written description requirement of 35 U.S.C. §112, since the patent described the compound's desired function of reducing activity of the enzyme PGHS-2 without adversely affecting PGHS-1 enzyme activity, but did not identify said compound, since invention consists of performing “assays” to screen compounds in order to discover those with desired effect. The patent did not name even one compound that assays would identify as suitable for practice of invention, or provide information such that one skilled in art could identify suitable compound. And since specification did not indicate that compounds are available in public depository, the claimed treatment method cannot be practiced without compound. Thus the inventors cannot be said to have “possessed” claimed invention without knowing of a compound or method certain to produce compound. Thus said patent constituted an invitation to experiment to first identify, then characterize, and then use a therapeutic a class of compound defined only by their desired properties.

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21. Therefore the full breadth of the claim fails to meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

Summary

22. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is **(571) 272-0889**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on **(571) 272-0887**.

The fax number for the organization where this application or proceeding is assigned is **703-872-9306**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).



CJN
April 21, 2004

ELIZABETH KEMMERER
PRIMARY EXAMINER